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Immune-mediated liver injury represented as overlap syndrome after SARS-CoV-2 vaccination

To the Editor:

We read an interesting article entitled "SARS-CoV-2 vaccination can elicit a CD8$^+$ T-cell dominant hepatitis" by Boettler *et al.*,[1] recently published in the *Journal of Hepatology*, demonstrating SARS-CoV-2-specific T-cell-dominant immune-mediated hepatitis after vaccination. This phenomenon may account for the association between SARS-CoV-2 vaccination and autoimmune hepatitis (AIH)-like conditions including overlap syndrome. Herein, we describe a case of overlap syndrome after SARS-CoV-2 vaccination.

Case: A 57-year-old woman without a history of medical diseases and taking hepatotoxic drugs or alcohol was referred to

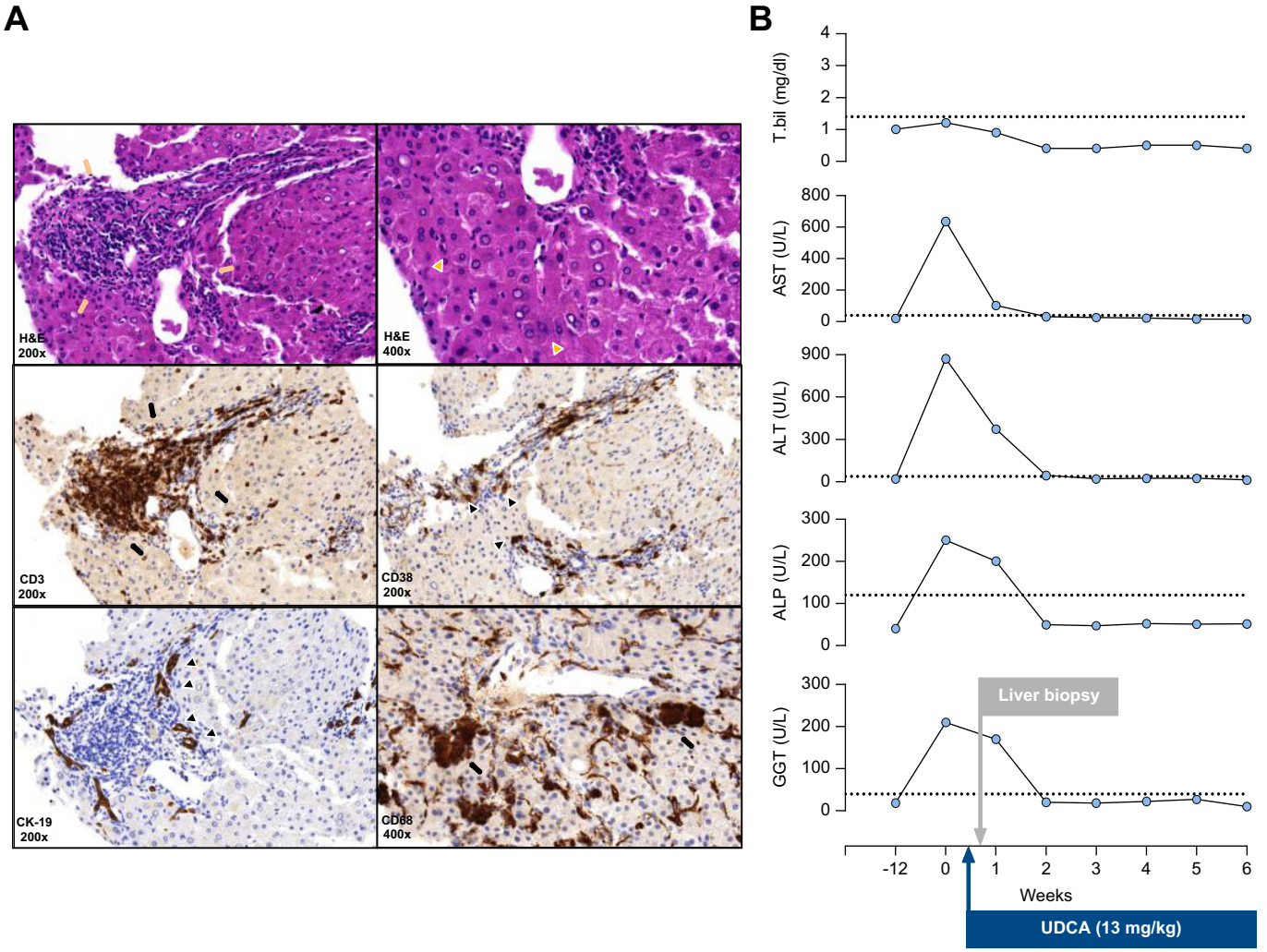

Fig. 1. Histopathological findings and clinical course of the patient. (A) On H&E staining, moderate-to-severe portal inflammation, piecemeal necrosis, interface hepatitis (left upper, yellow arrows), and rosette formation (right upper, yellow arrowhead) was noted. CD3$^+$ T-cell-dominant infiltration (left middle, black arrows) along with CD38$^+$ cells (right middle, black arrowhead) were also identified. Nonsuppurative and granulomatous cholangitis with destruction and proliferation of the bile duct was also noted on CK-19 (left lower, black arrowhead) and CD68 (right lower, black arrows) staining. (B) The patient was treated with high-dose UDCA (13 mg/kg), and laboratory findings normalized in 2 weeks. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; UDCA, ursodeoxycholic acid. (This figure appears in color on the web.)

Keywords: primary biliary cholangitis; COVID-19; autoimmune.
Received 1 May 2022; received in revised form 20 June 2022; accepted 25 June 2022; available online 08 July 2022
https://doi.org/10.1016/j.jhep.2022.06.029

the clinic for general weakness. She used to have normal liver function tests in a routine medical check-up. Two weeks after the first dose of SARS-CoV-2 Pfizer/BioNTech BNT162b2 mRNA vaccine, she started developing fatigue and general weakness. Her physical examination was normal; however, laboratory tests were significant for total bilirubin, 1.2 mg/dl; aspartate aminotransferase, 635 U/L; alanine aminotransferase, 870 U/L; alkaline phosphatase, 250 U/L; gamma-glutamyl transferase, 210 U/L; and international normalized ratio, 1.02. Laboratory results were negative for hepatitis A, B, C, and E, Epstein-Barr virus (EBV), cytomegalovirus, and herpes simplex virus (HSV) types 1 and 2. Autoantibody tests were positive for antinuclear antibody (ANA, 1:160; homogeneous pattern) and anti-mitochondrial M2 antibody (AMA-M2), while the test for anti-smooth muscle antibody was negative. The immunoglobulin G level was 1,532 mg/dl (normal range: 800–1,800 mg/dl). Abdominal ultrasound findings were normal, without evidence of abnormal findings in the biliary tract and liver. A percutaneous liver biopsy was performed, revealing moderate portal inflammation with $CD3^+$ T-cell-dominant infiltration along with $CD38^+$ cells suggesting plasma cells, interface hepatitis, rosette formation, and piecemeal necrosis. Moreover, nonsuppurative and granulomatous cholangitis with destruction and proliferation of the bile duct, was also noted, which was compatible with the findings of overlap syndrome (Fig. 1A).[2,3] Taken together, the revised original score for AIH was 13 (results ≥10 suggest probable AIH) and the Paris criteria for AIH-primary biliary cholangitis (PBC) overlap syndrome was satisfied.[4,5] After treatment with high-dose ursodeoxycholic acid (13 mg/kg), her laboratory findings normalized in 2 weeks (Fig. 1B).

Several reports have documented the possibility of an association between the development of AIH and SARS-CoV-2 vaccination or infection.[6,7] This association has been thought to be attributable to molecular mimicry between the spike protein S1 of SARS-CoV-2, a viral protein coded by the mRNA vaccine, and human tissue proteins.[8,9] Finally, Boettler *et al.*[1] successfully demonstrated that AIH-like conditions could be caused by activated $CD8^+$ T cells, including vaccine-induced spike-specific $CD8^+$ T cells. These novel findings provide insights into the strong association between the development of AIH-like hepatitis and SARS-CoV-2 vaccination, which can also be applied to our case.

In our patient, $CD3^+$ T cells were also dominant among the infiltrating inflammatory cells of the portal area. Although virus-specific $CD8^+$ T cells were not identified in our case, most of the infiltrated T cells might be SARS-CoV-2 specific $CD8^+$ T cells according to the results of Boettler *et al.*,[1] which could be attributable to the development of overlap syndrome in our case. Interestingly, in our patient, non-suppurative and granulomatous cholangitis with destruction and proliferation of the bile ducts was identified, suggesting the presence of combined PBC.[2,3,10] As PBC also develops with the interaction of immune and biliary pathways, including recruited $CD4^+$ and $CD8^+$ T cells,[10] SARS-CoV-2-specific $CD8^+$ T cells might have contributed to the development of overlap syndrome in our patient following SARS-CoV-2 vaccination. In conclusion, our case supports the notion that SARS-CoV-2-specific T cells can cause AIH-like conditions, including overlap syndrome, after SARS-CoV-2 vaccination.

Financial support

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF), funded by the Ministry of Education (No. 2021R1I1A1A01050954; S.K.L.). This work was also principally supported by a National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (2020R1A2C3011569; P.S.S.).

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Soon Kyu Lee: Study concept and design, data acquisition and interpretation, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. Jung Hyun Kwon: Acquisition of data. Nara Yoon and Sung Hak Lee: Analysis and interpretation of data. Pil Soo Sung: Study concept and design and critical revision of the manuscript for important intellectual content.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.06.029.

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Author names in bold designate shared co-first authorship

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Italian children seem to be spared from the mysterious severe acute hepatitis outbreak: A report by SIGENP Acute Hepatitis Group

To the Editor:

In the period April 5th-May 26th, 650 probable cases of severe acute hepatitis of unknown origin from 33 countries were reported to the World Health Organization (WHO).[1] So far, due to the absence of a defined aetiology, only either probable or epi-linked cases can be considered. According to the WHO, a probable case is defined as an individual aged 16 or younger presenting since 1 October 2021 with an acute hepatitis (non hep A-E) characterized by serum aminotransferases >500 IU/L (AST or ALT).[1] Although several pathogens have been isolated in the reported cases, none of them have been clearly demonstrated to be causal. In the absence of defined diagnostic criteria, it is very difficult to understand how the few cases of severe acute hepatitis reported in countries other than the UK have been assimilated to the latter. Despite the presumed infectious origin of the outbreak, there were no family clusters except for 2 children who were close contacts with 2 other cases.[2] Furthermore, in the reports available so far, an extensive evaluation of the non-infectious causes of acute hepatitis was not always carried out.[3,4] On the other hand, a trend towards the overestimation of cases following the emotional wave of the COVID-19 pandemic cannot be excluded.

A survey study was conducted by the liver group of the Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP) for a case estimation in Italy in the period January-May 2022 using a permanent mailing list that includes all the main paediatric liver units distributed throughout the country. The online survey aimed to explore the demographic and clinical features of the observed cases, the identified aetiologies, the diagnostic work-up, the outcome of the patients, and comparison with the previous 3 years.

On May 20, 27 Italian paediatric centres, including 4 paediatric liver transplant centres, reported on 44 patients. Six patients were excluded: 5 because of AST and ALT values <500 IU/L and 1 because they fell outside the study period. In 4/38 cases, a putative aetiology was later found: 2 autoimmune hepatitis (AIH), 1 coeliac disease in which the rise in transaminases was explained by an influenza infection (with AST and ALT decreasing before the start of the gluten free diet), and 1 myositis with liver involvement due to *Mycoplasma* infection. Among the 34 patients fulfilling inclusion criteria (median age 51.5 months, range 1-171), 18 (52.9%) aged <5 years, 24 (70.6%) were observed between March and May 2022. Only 2 cases had a recent travel history. The geographic distribution of the cases was: Northern Italy 17 (50%), Centre 8 (23.5%), Southern and Islands 9 (26.5%). The most frequent symptoms were: fever (52.9%), vomiting (47.1%), abdominal pain (38.2%), diarrhoea (26.5%), jaundice (20.6%), other (38.2%). Acute liver failure (international normalized ratio >2) was diagnosed in 3 patients.[5] HAV and HEV results were not available at the survey time in 17.6% and 58.8%, respectively. Notably, HEV infection is rarely observed in Italian children.[6] HBV and HCV infections were ruled out in 31 (91.2%) and 25 (73.5%) patients, respectively. HBV and HCV screening was probably not performed in the entire population because HBV mass vaccination has been implemented in Italian infants for many decades and HCV rarely shows an acute course.[7]

Four of 31 (12.9%) patients were vaccinated for SARS-CoV-2 (3 with 2 doses) supporting the absence of a role of the vaccine in triggering this condition. 38.2% had history of COVID-19 of whom 53.8% had it within the 3 months prior to observation.

Infectious agents were detected in 21/34 (61.8%) cases of which 12 (57.1%) showed multiple infections. In 9/21 patients, one or more potentially hepatotropic agents were identified: cytomegalovirus, Epstein-Barr virus, *Leishmania*, *E. Coli*, HHV6 and 7, Norovirus, Rotavirus. SARS-CoV-2 was positive in 4 (11.8%) patients. 26 patients were tested for Adenovirus and 6 (23.1%) were infected. None had SARS-CoV-2/Adenovirus co-infection. The other agents identified were Rhinovirus, Parvovirus, Metapneumovirus, Paraechovirus, Enterovirus, Influenza A, Coronavirus OC43, *Salmonella paratyphi*, *C. Difficile*, and *S. Pneumoniae.*

The results from our study suggest a poor association of SARS-CoV-2 and Adenovirus infection with severe acute hepatitis. This fits with the relatively small number of cases of severe acute hepatitis compared to the millions of people who have had COVID-19 in the context of the pandemic. The finding of multiple infectious agents in our patients with severe acute hepatitis, on the one hand, may reflect greater attention to the problem and, on the other, could be explained by an increased circulation of infections after 2 years of social restrictions. SARS-CoV-2, Adenovirus, Norovirus, Herpesvirus and other viruses have already been reported as possible causes of acute hepatitis, even if not so commonly.[8] Furthermore, Italian experience does not

Keywords: hepatitis; children; adenovirus; liver transplantation; acute liver failure.
Received 14 June 2022; accepted 15 June 2022; available online 07 July 2022
https://doi.org/10.1016/j.jhep.2022.06.026